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Internal Dynamics of Ribosomal Elongation Factors G and Tu Studied with All-Atom and Coarse-Grained Molecular Dynamics

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Translation is modulated by various protein factors interacting with the ribosome. Elongation factor Tu (EF-Tu) delivers the aminoacyl-tRNA to the ribosomal A-site. After the peptide bond is formed, elongation factor G (EF-G) facilitates translocation of tRNAs to prepare the ribosome for the next catalytic cycle. The structure of EF-G resembles that of the complex between EF-Tu and aminoacyl-tRNA. We apply all-atom and coarse-grained molecular dynamics to search for common internal motions of these two molecules.

1 Introduction

Protein synthesis on the ribosome involves a number of protein factors that bind at its different functional sites. Our work focuses on two GTP-driven factors which share a common binding site: elongation factor G (EF-G) and elongation factor Tu (EF-Tu). EF-Tu transports the aminoacyl-tRNA (aa-tRNA) to the aminoacyl binding site (A-site) of the ribosome, in the form of the ternary complex EF-Tu-GTP-aa-tRNA. EF-G promotes translocation of the newly synthesized peptidyl-tRNA from the A-site to the peptidyl-tRNA binding site (P-site) together with its associated mRNA¹. The structure of the EF-G resembles that of the complex between EF-Tu and aa-tRNA. This is an example of *molecular mimicry*²; a protein evolved so that its domains mimic the shape of a tRNA molecule. The N-terminal region of EF-G is homologous to EF-Tu, and the C-terminal region comprises a set of protein domains that adopted the shape of a tRNA¹. We describe and compare internal dynamics of both factors, using full-atom and coarse-grained molecular dynamics (MD). Our aim was to check whether any similarity exists also in the dynamical behavior of the EF-G and EF-Tu-aa-tRNA complex.

2 Methods

Full-atom MD simulations were performed with the Amber9 package (<http://amber.scripps.edu/>). Structures of EF-G and EF-Tu-aa-tRNA were described according to the AMBER2003 force field. Mesoscopic model of solvent (GB^{OBC} model³) was used with dielectric constants set to 1 for solutes and 80 for water. Simulations were conducted at 150mM ionic strength. The temperature, set to 293K, was controlled with Andersen scheme⁴. Non-bonded interaction cutoff distance was set to 18Å. To analyze 20ns full-atom MD trajectories we applied principal component analysis⁵ (PCA). Coarse-grained MD employed the Reduced Molecular Dynamics (RedMD)

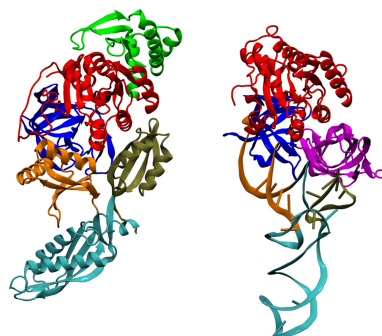


Figure 1. Left: the structure of EF-G (PDB code 1FNM⁷); red: domain I(G), green: insert (G'), blue: domain II, orange: domain III, cyan: domain IV, tan: domain V Right: the structure of EF-Tu:aa-tRNA complex (PDB code 1TTT⁸); red: domain I(G), blue: domain II, orange: the acceptor stem of aa-tRNA, cyan: the anticodon arm of aa-tRNA, tan: the T-arm of aa-tRNA. Domains I(G) and II of the EF-Tu and EF-G are homologous and common for GTPases¹.

package⁶, a novel software which has been recently developed in our laboratory, with protein residues and RNA nucleotides represented as beads, interacting through harmonic (for neighboring) or Morse (for nonbonded) potentials⁶. Dynamics was simulated using Langevin equation (293K) and 1 μ s trajectory were generated for each molecule.

3 Results

Figure 2 presents correlation matrices derived from full-atom MD trajectories. For both molecules, motions of residues from distinct domains are correlated and the magnitude of this correlation is similar for homologous domains I and II. Strongest correlation occurs for

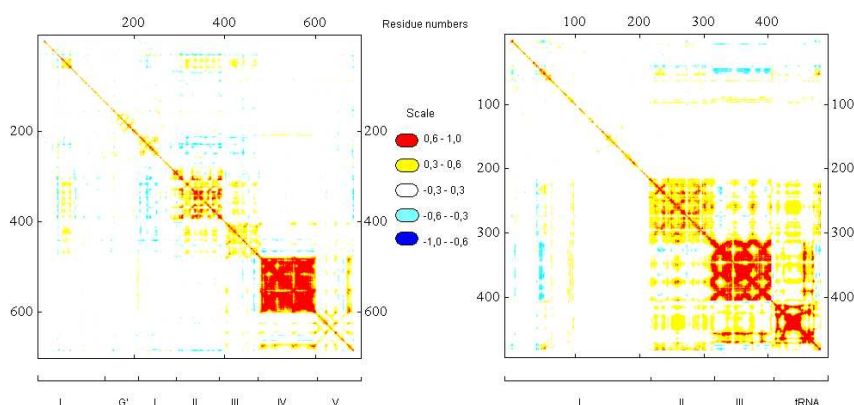


Figure 2. Correlation matrices: EF-G (left) and EF-Tu-aa-tRNA (right).

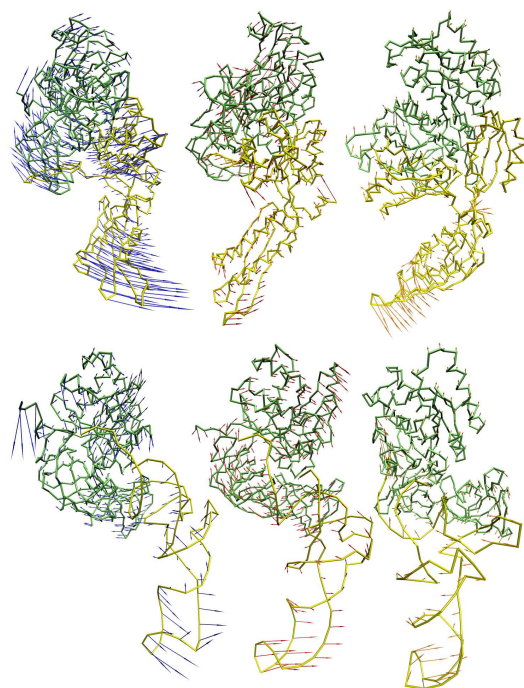


Figure 3. Graphical representation of collective motions in EF-G (top) and EF-Tu-aa-tRNA (bottom). Domains III, IV and V of EF-G and aa-tRNA are marked in yellow. Arrows show the directions of the first three eigenvectors of PCA analysis.

residues of domain IV of EF-G and domain III of EF-Tu-aa-tRNA complex. Three groups (the T arm, the acceptor stem and anticodon loop) are distinguishable in the nucleic part of the EF-Tu-aa-tRNA complex with strongly correlated movements of nucleotides within each group.

To characterize the most significant collective modes of motions we applied PCA to full-atom MD trajectories (Figure 3). The most dominant motions are those of domains III, IV and V of EF-G and those of aa-tRNA of EF-Tu-aa-tRNA complex. In both cases, the first two PCA principal components describe pendulum-like motions (in different planes) of the three EF-G domains and aa-tRNA, relative to the homologous domains I and II. Third PCA eigenvector describes pendulum-like motions of EF-G domains but for EF-Tu-aa-tRNA a stretching mode is also seen. We also compared the internal dynamics obtained with full-atom and coarse-grained MD. Figure 4 shows that root mean square fluctuations (RMSF) of C_{α} (EF-G) and C_{α} and P atoms (EF-Tu-aa-tRNA) observed in full-atom and coarse-grained simulations are of similar magnitude.

4 Conclusions

We compared internal dynamics of two structurally similar systems: protein EF-G and protein:RNA complex (EF-Tu-aa-tRNA) applying full-atom and coarse-grained MD. Our study demonstrated a certain degree of similarity in their dynamics, however, still more

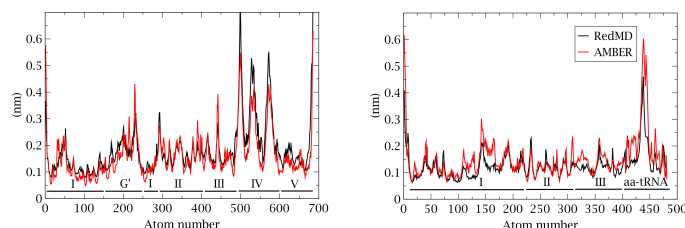


Figure 4. RMSF of C_{α} (EF-G, left) and C_{α} and P atoms (EF-Tu-aa-tRNA, right) derived from full-atom and coarse-grained MD simulations.

work is required to investigate its character⁹.

Acknowledgments

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